that may be an allelic variant or a heterospecific homologue. Claim 50 has been amended to recite a host cell that was been transformed *in vitro* with certain expression vectors. That amendment is supported in the specification at page 30, lines 1-15. Claims 118 and 120 have been amended to recite a "composition." Attached is a marked-up copy of the amended claims, as well as a clean copy of the complete set of pending claims as amended. No new matter is introduced by those amendments.

Remarks

Claims 1-11, 38-54, 62 and 118-120 were considered in the Office Action of February 21, 2001. Certain of the claims were objected to for containing subject matter drawn to a non-elected species. In addition, certain of the claims were rejected under 35 U.S.C. § 112, first and second paragraphs, and 35 U.S. C. 102 over Hillier et al., (1995). Applicants address the objection and rejections below inasmuch as they may apply to the claims as amended.

1. The Objection

Claims 1-11, 38-54, 62 and 118-120 were objected to as containing subject matter drawn to a non-elected invention. In response, Applicants have canceled claims 1, 3, 8, 10, and 119, and amended the remaining claims in order to limit the claimed subject matter to the elected invention. As such, Applicants respectfully request that the objection be reconsidered and withdrawn.

2. The Rejections Under 35 U.S.C. § 112, First Paragraph

Each of claims 1-4, 8-11, 38, 39, 45, 48-54, 62, and 118-120 stands rejected under 35 U.S.C. § 112, first paragraph. Specifically, certain of those claims were said to recite proteins and isolated nucleic acids that were not enabled by the specification because no guidance was provided in the claims as to what would constitute the recited protein or nucleic acid. Applicants have amended the claims to recite specific sequences by identification number. As such, Applicants respectfully submit no under experimentation would be required of one skilled in the art to practice the invention as claimed and described in the specification.

Further, the terms "allelic variant" and "homologue," as recited in claims 38 and 39, were said to be insufficiently described in the specification because there is no detailed description of the structure of these elements. Applicants have amended claims 38 and 39 to recite a "variant" sequence of a gene or protein which is specifically identified by reference to a sequence identification number. The term "variant," as used in reference to a sequence, is defined at page 20, lines 1-10, of the specification in terms of primary structure. For example, at lines 7-10, Applicants teach that variant sequences are at least 70-80% similar, or 60-70% identical to a disclosed sequence. As such, Applicants respectfully submit that claims 38 and 39, as amended, are sufficiently described in the specification.

Claims 50-54 were said to recite a host cell that was not enabled in the specification because the specification was said not to teach how to transfect a cell *in vivo*. Applicants have amended claim 50, from which claims 51-54 depend, to recite a host cell that is been transformed *in vitro*. Applicants respectfully submit that methods of producing appropriate vectors, transforming cells with those vectors *in vitro*, and identifying transformed cells are well known in the art (see page 30, lines 10-14 of the specification), and that no undue experimentation would be required to practice the invention as claimed in claims 50-54, as amended. As such, Applicants respectfully submit that those claims are enabled in the specification.

Finally, claims 118-120 were said to contain subject matter that was not enabled in the specification. Specifically, the specification was said to fail to adequately teach how to effectively treat a disease or reach any therapeutic endpoint by administering the recited vectors or sequences. Claims 118 and 120 have been amended to delete reference to a "pharmaceutical preparation," and now recite a "composition." As such, Applicants respectfully submit that the basis of this rejection has been obviated.

For the reasons discussed above, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

3. *The Rejections Under 35 U.S.C. § 112, Second Paragraph*

Claims 1-4, 8-11, 38, 39, 45, 48-54, 62, and 118-120 were rejected as being indefinite in the recitation of a gene or protein by an arbitrary name. Applicants have amended those claims to include reference to specific sequences by identification number. As such, Applicants respectfully submit that this rejection should be withdrawn.

4. *The Rejection Under 35 U.S.C. § 102*

Claims 5-7 were rejected under 35 U.S.C. § 102 over Hillier et al. (1995). Anticipation under 35 U.S.C. §102 requires that a single reference teach each and every element of a claim. Verdegaal Bros. v. Union Oil Co. of California, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Claims 5-7, as amended, recite consecutive nucleotides of specific regions of the claimed sequence that are not taught by Hillier et al. As such, Applicants respectfully request that Hillier et al. does not anticipate those claims under 35 U.S.C. § 102, and that the rejection thereunder should be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that the claims are now in condition for allowance. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number below.

Respectfully submitted,

5/17/01
Date:

Jennifer A. Camacho
Attorney for Applicants
Reg. No. 43,526

Testa, Hurwitz & Thibeault, LLP
High Street Tower
125 High Street
Boston, MA 02110
(617) 248-7476

MIT-103

U.S.S.N. 09/422,999 - Filed 10/22/99

CLAIM AMENDMENTS IN MARK-UP FORMAT

1. (Canceled)

2. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding a protein selected from the group consisting of [a normal cAMP-GEFI protein, a mutant cAMP-GEFI protein,] an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO: 18, a normal variant of said hcAMP-GEFII protein, and a mutant of said hcAMP-GEFII protein.

3. (Canceled)

4. (Amended) An isolated nucleic acid as in claim 2 wherein said nucleic acid encodes a normal variant of said hcAMP-GEFII protein and wherein said nucleotide sequence comprises a sequence encoding a normal variant of said hcAMP-GEFII protein and capable of hybridizing under stringent hybridization conditions to a sequence complementary to [is selected from the group consisting of

(a) a sequence encoding a protein comprising the human cAMP-GEFI amino acid sequence of SEQ ID NO: 12;

(b) a sequence encoding a protein comprising the alternatively spliced human cAMP-GEFI amino acid sequence of SEQ ID NO: 14;

(c) a sequence encoding a protein comprising the rat cAMP-GEFI amino acid sequence of SEQ ID NO: 10;

(d)]a sequence encoding a protein comprising the human cAMP-GEFII amino acid sequence of SEQ ID NO: 18[;

(e) a sequence encoding a protein comprising the rat cAMP-GEFII amino acid sequence of SEQ ID NO: 16; and

(f) a sequence encoding a normal cAMP-GEF protein and capable of hybridizing to a sequence complementary to any sequence of (a) - (e) under stringent hybridization conditions].

5. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 8 consecutive nucleotides selected from the group consisting of [SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15,] (a) nucleotides 1-2600 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2600 of SEQ ID NO. 17[any of these sequences].

6. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides selected from the group consisting of [SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15,] (a) nucleotides 1-2602 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2602 of SEQ ID NO: 17.

7. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 15 consecutive nucleotides selected from the group consisting of [SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15,] (a) nucleotides 1-2607 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2607 of SEQ ID NO. 17 .

8. (Canceled)

9. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding at least one functional domain of [a cAMP-GEF protein selected from the group consisting of a normal cAMP-GEFI protein,] an hcAMP-GEF II protein having the amino acid sequence of SEQ ID NO. 18; a normal variant of said hcAMP-GEFII protein, [a mutant cAMP-GEFI protein,] [and] or a mutant of said hcAMP-GEFII protein.

10. (Canceled)

11. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding an antigenic determinant of [a] an hcAMP-GEFII protein (SEQ ID NO: 18) and selected from the group consisting of [a normal cAMP-GEFI protein,] a normal variant of said hcAMP-GEFII protein, [a mutant cAMP-GEFI protein,] and a mutant of said hcAMP-GEFII protein.

38. (Amended) An isolated nucleic acid comprising a variant nucleotide sequence of a human cAMP-GEFII gene (SEQ ID NO: 17), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEFII gene, and [or]a heterospecific homologue of [a]said [gene selected from the group consisting of a human CalDAG-GEF gene, and a]human cAMP-GEFII gene.

39. (Amended) An isolated nucleic acid encoding a variant amino acid sequence of a human cAMP-GEFII protein (SEQ ID NO: 18), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEFII, and a[or] heterospecific homologue of said[a protein selected from the group consisting of a human CalDAG-GEF protein, and a] human cAMP-GEFII protein.

40. (Amended) An isolated nucleic acid comprising a recombinant vector including a nucleotide sequence selected from the group consisting of [SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15,] SEQ ID NO: 17, and a sequence complementary to SEQ ID NO: 17.

45. (Amended) An isolated nucleic acid as in claim 41 wherein said expression vector encodes at least a functional domain of a protein selected from the group consisting of [normal CalDAG-GEFI, a normal CalDAG-GEFII, a mutant CalDAG-GEFI, a mutant CalDAG-GEFII, a normal cAMP-GEFI,] an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO:

18, a normal variant of said hcAMP-GEFII, [a mutant cAMP-GEFI,] and a mutant of said hcAMP-GEFII.

48. (Amended) An isolated nucleic acid comprising a recombinant expression vector including nucleotide sequences corresponding to an endogenous regulatory region of [a gene selected from the group consisting of a CalDAG-GEF gene, and] an hcAMP-GEFII gene (SEQ ID NO. 17).

50. (Amended) A host cell comprising [transformed with] an expression vector of any one of claims 41-49, or a descendant thereof, wherein said host cell is transformed *in vitro* with said expression vector.

62. (Amended) A method for producing at least a functional domain of [a protein selected from the group consisting of a CalDAG-GEF protein, and a] an hcAMP-GEFII protein (SEQ ID NO: 18), said method comprising culturing a host cell of any of claims 50-54 under suitable conditions to produce said protein by expressing said nucleic acid.

118. (Amended) A composition [pharmaceutical preparation] comprising an expression vector operably encoding [a protein selected from the group consisting of a CalDAG-GEF protein, and a] an hcAMP-GEFII protein (SEQ ID NO: 18) or a normal variant thereof, wherein said expression vector may express said [CalDAG-GEF protein or said] hcAMP-GEFII protein or normal variant in a human subject, and a pharmaceutically acceptable carrier.

119. (Canceled)

120. (Amended) A composition [pharmaceutical preparation] comprising an expression vector operably encoding an antisense sequence of an hcAMP-GEFII gene (SEQ ID NO: 17) [antisense sequence], wherein said expression vector may express said [cAMP-GEF] antisense sequence in a human subject, and a pharmaceutically acceptable carrier.

MIT-103

U.S.S.N. 09/422,999 - Filed 10/22/99

CLEAN COPY OF CLAIMS

1. (Canceled)

2. An isolated nucleic acid comprising a nucleotide sequence encoding a protein selected from the group consisting of an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO: 18, a normal variant of said hcAMP-GEFII protein, and a mutant of said hcAMP-GEFII protein.

3. (Canceled)

4. (Amended) An isolated nucleic acid as in claim 2 wherein said nucleic acid encodes a normal variant of said hcAMP-GEFII protein and wherein said nucleotide sequence comprises a sequence encoding a normal variant of said hcAMP-GEFII protein and capable of hybridizing under stringent hybridization conditions to a sequence complementary to a sequence encoding a protein comprising the human cAMP-GEFII amino acid sequence of SEQ ID NO: 18.

5. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 8 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2600 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2600 of SEQ ID NO. 17.

6. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2602 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2602 of SEQ ID NO: 17.

7. (Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 15 consecutive nucleotides selected from the group consisting of (a) nucleotides 1-2607 of SEQ ID NO. 17, and (b) a sequence complementary to nucleotides 1-2607 of SEQ ID NO. 17 .

8. (Canceled)

9. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding at least one functional domain of an hcAMP-GEF II protein having the amino acid sequence of SEQ ID NO. 18; a normal variant of said hcAMP-GEFII protein, or a mutant of said hcAMP-GEFII protein.

10. (Canceled)

11. (Amended) An isolated nucleic acid comprising a nucleotide sequence encoding an antigenic determinant of an hcAMP-GEFII protein (SEQ ID NO: 18) and selected from the group consisting of a normal variant of said hcAMP-GEFII protein, and a mutant of said hcAMP-GEFII protein.

38. (Amended) An isolated nucleic acid comprising a variant nucleotide sequence of a human cAMP-GEFII gene (SEQ ID NO: 17), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEF II gene, and a heterospecific homologue of said human cAMP-GEFII gene.

39. (Amended) An isolated nucleic acid encoding a variant amino acid sequence of a human cAMP-GEFII protein (SEQ ID NO: 18), said variant being selected from the group consisting of an allelic variant of said human cAMP-GEF II protein, and a heterospecific homologue of said human cAMP-GEFII protein.

40. (Amended) An isolated nucleic acid comprising a recombinant vector including a nucleotide sequence selected from the group consisting of SEQ ID NO: 17, and a sequence complementary to SEQ ID NO: 17.

41. An isolated nucleic acid as in claim 40 wherein said vector is an expression vector and said nucleotide sequence is operably joined to a regulatory region.

42. An isolated nucleic acid as in claim 41 wherein said expression vector may express said nucleotide sequence in mammalian cells.

43. An isolated nucleic acid as in claim 42 wherein said cells are selected from the group consisting of fibroblast, liver, kidney, spleen, bone marrow, and neurological cells.

44. An isolated nucleic acid as in claim 42 wherein said vector is selected from the group consisting of vaccinia virus, adenovirus, retrovirus, neurotropic viruses, and Herpes simplex.

45. (Amended) An isolated nucleic acid as in claim 41 wherein said expression vector encodes at least a functional domain of a protein selected from the group consisting of an hcAMP-GEFII protein having the amino acid sequence of SEQ ID NO: 18, a normal variant of said hcAMP-GEFII, and a mutant of said hcAMP-GEFII.

46. An isolated nucleic acid as in claim 41 wherein said vector further comprises sequences encoding an exogenous protein operably joined to said nucleotide sequence and whereby said vector encodes a fusion protein.

47. An isolated nucleic acid as in claim 46 wherein said exogenous protein is selected from the group consisting of lacZ, trpE, maltose-binding protein, poly-His tags, and glutathione-S-transferase.

48. (Amended) An isolated nucleic acid comprising a recombinant expression vector including nucleotide sequences corresponding to an endogenous regulatory region of an hcAMP-GEFII gene (SEQ ID NO. 17).

49. An isolated nucleic acid as in claim 48 wherein said endogenous regulatory region is operably joined to a marker gene.

50. (Amended) A host cell comprising an expression vector of any one of claims 41-49, or a descendant thereof, wherein said host cell is transformed *in vitro* with said expression vector.

51. A host cell as in claim 50 wherein said host cell is selected from the group consisting of bacterial cells and yeast cells.

52. A host cell as in claim 50 wherein said host cell is selected from the group consisting of fetal cells, embryonic stem cells, zygotes, gametes, and germ line cells.

53. A host cell as in claim 50 wherein said cell is selected from the group consisting of fibroblast, liver, kidney, spleen, bone marrow and neurological cells.

54. A host cell as in claim 50 wherein said cell is an invertebrate cell.

62. (Amended) A method for producing at least a functional domain of an hcAMP-GEFII protein (SEQ ID NO: 18), said method comprising culturing a host cell of any of claims 50-54 under suitable conditions to produce said protein by expressing said nucleic acid.

118. (Amended) A composition comprising an expression vector operably encoding an hcAMP-GEFII protein (SEQ ID NO: 18) or a normal variant thereof, wherein said

expression vector may express said hcAMP-GEFII protein or normal variant in a human subject, and a pharmaceutically acceptable carrier.

119. (Canceled)

120. (Amended) A composition comprising an expression vector operably encoding an antisense sequence of an hcAMP-GEFII gene (SEQ ID NO: 17), wherein said expression vector may express said antisense sequence in a human subject, and a pharmaceutically acceptable carrier.